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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/594,597	IKEDA ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 14-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 14-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/28/06; 12/28/06; 3/7/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-8 and 14-21 are pending and examined on the merits.

Election/Restrictions

1. Applicant's election without traverse of the invention of Group 1 (methods of evaluating drug sensitivity) in the reply filed on 02/26/2009 is acknowledged. Applicants' further election of Haplotype No.5 from Table 8 of the specification is also acknowledged.

Claim Objections

2. Claims 1-8 and 14-21 are objected to for the requirement and specific recitation of non-elected subject matter in the alternative. Applicants have elected for the examination of claims as they require the particular haplotype AGAC as disclosed in Table 8 of the specification. The AGAC haplotype consists of position A118G, IVS2 +G691C, IVS3 +A6151G, and IVS3 +C8497T, where Table 4 indicates that the haplotype thus consists of the particular combination of SEQ ID NO: 15, 24, 28, and 30. However, the claims recite any combination of sequences selected from SEQ ID NO: 1-15, 16-25, 26, 27, and 28-98. It is noted that no claim is allowed in this Office Action. Prior to the allowance of any claim, non-elected subject matter that is not rejoined with the elected combination and also allowed will be required to be deleted from the claims.

Claims 1 and 14 are objected to over recitation of the phrase 'gene polymorphisms that are linkage disequilibrium', where the phrase 'gene polymorphisms that are in linkage disequilibrium' is correct

Appropriate corrections are required.

Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 5-8 and 18-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5, 6, 18 and 19 are unclear over references to tables from the specification as recited in the claims. MPEP 2173.05(s) provides:

> Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).

In the instant case polymorphisms and haplotypes can be indicated by inclusion of particular sequences as identified by SEQ ID NO: from the sequence listing.

Claims 7, 8, 20, and 21 are unclear over the purpose of the claimed methods for 'determining a type and/or amount of a drug to be administered' (as recited in claims 7 and 20) and 'predicting a side effect of a drug to be administered' (as recited in claims 8

and 20). There are no method steps recited or required in the rejected claims where the performance of such steps results in accomplishing the claimed method. It is thus unclear as to how the purpose of the claimed methods are accomplished. The rejected claims are further unclear over recitation of the phrase 'by using as an index, a result', as recited in each of the rejected claims. There is no recitation in the claims as to how an index is used to accomplish the purpose of the claimed methods.

Claim 14 is unclear over the stated purpose of the claimed method as 'a diagnostic method of an administered does', as it is unclear what a 'method of an administered dose' is. The single method step requires only 'linking a haplotype to individual drug sensitivity', but there is nothing in this active step that requires any 'administered dose', nor is it clear what is diagnosed.

Claim Rejections - 35 USC § 112 1st¶ - Written Description

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 14-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants are directed to the Written Description Training Materials revised March 25, 2008, available online at http://www.uspto.gov/web/menu/written.pdf.

The rejection of claims for lack of adequate written description is relevant the requirement of the claims for a 'haplotype being estimated from gene polymorphisms that are linkage disequilibrium' in methods for evaluating drug sensitivity (e.g. claim 1) and diagnosing an administered dose' (e.g. claim 14). In the instant case the specification does not provide the skilled artisan with an adequate written description of haplotypes that are in linkage disequilibrium with the AGAC haplotype No. 5 of Table 8 (As consonant with the Election).

The specification provides no limiting structures as to what nucleotide content of gene polymorphisms in a particular degree of linkage disequilibrium are required to estimate the Elected haplotype as required by the claims. Thus when the claims are analyzed in light of the specification, the claims encompass a large genus of nucleotide contents in a variety of sequence contexts.

Relevant to the lack of particular structural limitations in the rejected claims, MPEP 2163 states:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art.

In the instant claims, the a priori identification of particular nucleotide content that is in linkage disequilibrium with, and thus may 'estimate', the required haplotype is critical to the claimed invention. However, given the particular recitations in the claims

and the lack of limiting structural requirements of the required polymorphisms in the specification, one of skill in the art can not a priori identify the required polymorphisms. For example, while Table 6 of the specification indicates a significant D' value of 1.000 for linkage between IVS3 +5807 and IVS2 +691, the same table indicates an insignificant r^2 value of 0.134 for the same polymorphisms. The difficulty in identifying markers that are in linkage disequilibrium is demonstrated by the prior art of Wall et al (2003), which teaches (p.587 - Linkage disequilibrium) that patterns of LD are well known for being noisy and unpredictable. For example, pairs of sites that are tens of kilobases apart might be in 'complete' LD, whereas nearby pairs of sites from the same region might be in weak LD. Similarly, there can be tremendous differences in the extent of LD from one genomic region to another.

In conclusion, having considered the breadth of the claims, the particular teachings of the instant specification, and the teachings of the prior art, the specification, while providing a written description of (as consonant with the Election) methods requiring:

> Detection of a human mu opioid receptor haplotype, said haplotype comprising:
> SEQ ID NO: 15, wherein position 51 of SEQ ID NO: 15 is an A;
> SEQ ID NO: 24, wherein position 51 of SEQ ID NO: 24 is a G;
> SEQ ID NO: 28, wherein position 51 of SEQ ID NO: 28 is an A; and
> SEQ ID NO: 30, wherein position 51 of SEQ ID NO: 30 is a C.

does not does not provide an adequate written description of gene polymorphisms that are in linkage disequilibrium as required to estimate a haplotype.

Claim Rejections - 35 USC § 112 1st ¶ - Enablement

6. Claims 1-8 and 14-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

The instant claims are drawn to methods of evaluating drug sensitivity (as recited in claim 1) and diagnosing an administered dose (as recited in claim 14), and require detection of a haplotype.

The claims further encompass methods of determining type or amount of drug to be administered (claim 7 and 20), and predicting side effects (claim 8 and 21).

The claims encompass diagnostic methods in any subject organism.

The claims require knowledge of a correlative association between a haplotype and a wide variety of phenotypic qualities.

Direction provided by the specification and working example

The instant specification provides an example (e.g.: p.13) of the identification of polymorphisms in the human mu opioid receptor (Tables 1, 2, and 4), and several haplotypes of some particular polymorphisms (e.g.: Table 5). The instant specification provides an analysis of linkage disequilibrium of mu opioid receptor polymorphisms (Table 6).

The specification asserts (e.g. p.12-13) that analyzing haplotypes makes it possible for one to elucidate drug sensitivity, and thus allows one to know in advance an

appropriate amount of drug to be administered to an individual before administering the drug. The only analysis of any association of between the elected haplotype (i.e. haplotype No. 5 of Table 8) and a phenotype is an analysis of haplotype frequency in patients addicted to methamphetamines as compared to haplotype distribution in non-addicted subjects (p.52 – Example 4).

The specification does not provide any analysis of any non-human subjects.

The instant specification provides no analysis of any associations between haplotypes and drug side effects.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art with regard to the detection of any particular haplotype in a known gene is high, the unpredictability with regard to the association of any particular haplotype with a particular phenotype, the identification of any nucleotide sequence has having a particular functionality, and the estimation of any haplotype using different polymorphisms is even higher. The unpredictability is demonstrated by the prior art and the post-filing art, and the instant specification.

Because the claims encompass diagnostic methods in any subject organism, whereas the specification provides only an analysis of human subjects, it is relevant to point out the unpredictability in extrapolating the presence of polymorphic nucleotide content, or its association with any phenotype, form organism to any other different organism. Such unpredictability in interspecies extrapolation is addressed by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and

human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S).

Because the claims are drawn to methods that encompass the detection of any polymorphisms to estimate any haplotype, whereas the specification teaches only the detection of a particular mu opioid receptor haplotypes, it is relevant to point out the unpredictability in associating any sequence variation with a particular phenotype. For example, Hacker et al (1997) teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (pages 623-627). And while the claims encompass methods requiring estimation of any haplotype based on polymorphism detection, it is relevant to point out that the instant specification teaches the unpredictability in extrapolating phenotypic associations (as required by the claims) among different polymorphic content asserted to be in linkage disequilibrium. For example, while Table 6 asserts a significant (D' > 0.7) linkage disequilibrium between IVS2 +691 and A118G, this assertion is not supported by the data in Table 7 which asserts an association between IVS2 +691 and methamphetamine addiction but no significant association between A118G and the same phenotype.

Given the breadth of the claims as encompassing any polymorphisms in any level of linkage disequilibrium to estimate any haplotype, it is relevant to point out the unpredictability in associating any particular gene mutation with a particular phenotype. This is particularly true where the instant claims encompass sensitivity to any drug and

any side effects to any drug. As evidence of the unpredictability of gene association studies, Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph). Additionally, Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

With particular regard to associations with polymorphisms in the mu opioid receptor, the prior art and post-filing art indicate the unpredictability in establishing robust and reliable associations that are consistently accurate in dragonesses. For example, Coller et al teaches a meta analysis of the A118G SNP, where a thorough analysis indicates a lack of association between the polymorphism and opioid dependence, even where such an association was previously asserted in several

populations. Similarly, while the instant specification asserts an associaition between IVS2 +691 and methamphetamine addiction (Table 7), and the claims generically encompass and specifically recite ethanol (e.g. claim 3) as a drug for the claimed methods, Bergen et al teaches that there is no significant association between IVS2 +691 and alcohol dependence.

Finally, with regard to the specifically Elected haplotype (and in fact all the haplotypes of Table 8 and the analysis of methamphetamine addiction) it is relevant to point out that the specification (p.56-57) teaches that none of the associations were statistically significant, with a p-value of p=0.40. Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant (Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion).

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to make and use the claimed invention. Such experimentation would include large case:control studies in multiple populations of any subject organism of interest to demonstrate a reliable association of any different haplotype, as estimated by different polymorphisms, with sensitivity to any drug. One would have to perform large case:control studies to establish whether or any associations are reliable and robust. Such experimentation would be extensive, especially considering in the lack of data

presented in the instant specification regarding haplotypes and drug sensitivity. Even if one were to carry out such experimentation, there is no assurance that a reliable and consistent association of haplotypes and drug sensitivity would be identified.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance provided by the applicant and the specific examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention.

Conclusion

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Stephen Kapushoc/
Art Unit 1634